Effects of acute (-)-hydroxycitrate supplementation on substrate metabolism at rest and during exercise in humans

Effects of acute (−)-hydroxycitrate supplementation on substrate metabolism at rest and during exercise in humans[1,2]

Luc JC van Loon, Johannes JM van Rooijen, Bas Niesen, Hans Verhagen, Wim HM Saris, and Anton JM Wagenmakers

ABSTRACT

Background: (−)-Hydroxycitrate (HCA), a competitive inhibitor of ATP-citrate lyase, should reduce the extramitochondrial acetyl-CoA pool. It has been hypothesized that HCA ingestion can reduce malonyl-CoA concentrations and consequently increase fatty acid oxidation in vivo.

Objective: This study investigated the acute effects of HCA supplementation on substrate utilization at rest and during exercise in endurance-trained humans.

Design: Ten cyclists [($\bar{x}$ ± SD) age: 24 ± 2 y, weight: 73 ± 2 kg, maximal oxygen uptake: 4.95 ± 0.11 L/min, maximal work output (*W*max): 408 ± 8 W] were studied at rest and during 2 h of exercise at 50% *W*max on 2 occasions. Both 45 and 15 min before exercise and 30 and 60 min after the start of exercise, 3.1 mL/kg body wt of an HCA solution (19 g/L) or placebo was ingested. Total fat and carbohydrate oxidation rates were assessed. Blood samples were collected at 15-min intervals at rest and every 30 min during exercise.

Results: Plasma HCA concentrations increased after HCA ingestion up to 0.39 ± 0.02 mmol/L (82.0 ± 4.8 mg/L). However, no significant differences in total fat and carbohydrate oxidation rates were observed between trials. Accordingly, plasma glucose, glycerol, and fatty acid concentrations did not differ between trials. Plasma lactate concentrations were significantly lower in the HCA than in the placebo trial after 30 min of exercise but at the end of the exercise period they did not differ between trials.

Conclusion: HCA, even when provided in large quantities, does not increase total fat oxidation in vivo in endurance-trained humans. *Am J Clin Nutr* 2000;72:1445–50.

KEY WORDS (−)-Hydroxycitrate, HCA, *Garcinia cambogia*, fat oxidation, obesity, dietary supplement, weight loss

INTRODUCTION

Recently, a lot of publicity has been generated concerning a compound known as (−)-hydroxycitrate (HCA). HCA is being promoted as the new natural aid to losing weight and many promises about its effect on metabolism and appetite are being made.

HCA is a principal constituent in the rind of the fruit of *Garcinia cambogia*, which is used in the preparation of curries and condiments in Asian cuisine. HCA appears to be well tolerated and has a chemical structure much like that of citric acid. Consequently, HCA is now added extensively to a wide variety of nutritional supplements. Although the toxicologic safety of HCA is often stated, we are not familiar with published studies that actually investigated the safety (short- or long-term) of HCA supplementation. The knowledge that HCA could have an important effect on metabolism is not new—Sullivan and coworkers were already doing research on HCA in the 1970s (1–8). Although the clinical relevance of HCA as an effective antiobesity agent has often been proposed (1, 9–12), very little research has been performed to investigate the metabolic effects of HCA supplementation in vivo in humans.

HCA is a competitive inhibitor of ATP-citrate lyase (EC 4.1.3.8), the enzyme catalyzing the extramitochondrial cleavage of citrate to oxaloacetate and acetyl-CoA (5, 8, 13, 14). The action of HCA should reduce the acetyl-CoA pool, thus limiting the availability of 2-carbon units required for fatty acid and cholesterol biosynthesis. This has led to suggestions that HCA administration could inhibit lipogenesis. This was confirmed by several studies in which HCA administration (predominantly in rodents) inhibited the in vivo and in vitro rates of lipogenesis in several tissues known to convert carbohydrate into fatty acids, namely liver, adipose tissue, and small intestine (2, 4, 6–8, 15–17). HCA administration could also have an effect on fatty acid oxidation itself. Because extramitochondrial cleavage of citrate is the penultimate step in the conversion of glucose to malonyl-CoA, suggestions have been made that administration of HCA, by reducing the acetyl-CoA concentration, could reduce cytosolic malonyl-CoA concentrations and increase fatty acid oxidation (18–21). In support of this hypothesis, Chen et al (22) observed an increase in [1–1-^{4}C]palmitate oxidation rate in isolated islets from rat pancreas when perfused with HCA.

The implication of the latter mechanisms, when operative in vivo, is that HCA could be useful as a metabolic antiobesity agent. In addition, HCA supplementation has also been suggested as an ergogenic aid, especially because an increase in fat oxidative

[1] From the Nutrition and Toxicology Research Institute (NUTRIM), Department of Human Biology, Maastricht University, Maastricht, Netherlands, and the TNO Nutrition and Food Research Institute, Food and Supplement Analysis Department, Zeist, Netherlands.

[2] Address reprint requests to LJC van Loon, Department of Human Biology, Maastricht University, PO Box 616, 6200 MD Maastricht, Netherlands. E-mail: l.vanloon@hb.unimaas.nl.

Received January 10, 2000.

Accepted for publication May 15, 2000.

capacity would limit endogenous carbohydrate utilization during aerobic exercise (20, 21). Suggestions have also been made that increases in malonyl-CoA lead to insulin resistance in diabetic mice models (23). As such, a nutritional compound that could lower muscle malonyl-CoA concentration and increase fat oxidation would be extremely important. To date, only one recent study has investigated the effects of a small dose of HCA on total fat oxidation in humans (24). However, there are no data available that provide information about intestinal absorption and plasma availability after HCA supplementation. Therefore, no conclusions on the potential of HCA to increase muscle fat oxidation can be made.

This study investigated the acute effects of ingestion of HCA (6–30 times the reported dosage applied in human weight-loss studies) on plasma HCA availability. We further investigated whether systemic HCA availability altered fat oxidation rates and plasma metabolite concentrations at rest and during moderate-intensity exercise in endurance-trained humans.

SUBJECTS AND METHODS

Subjects

Ten cyclists [($\bar{x} \pm$ SD) age: 24.4 ± 1.6 y, height: 1.82 ± 0.02 m, weight: 73.2 ± 1.8 kg, body mass index (BMI; in kg/m^2): 22.1 ± 0.5, maximal oxygen uptake ($\dot{V}O_2$max): 4.95 ± 0.1 L/min, maximal work output (*W*max): 408 ± 8 W] participated in the study. All subjects were informed about the nature and putative risks of the experimental procedures before their informed consent was obtained. This study was approved by the local Ethical Committee of the Academic Hospital Maastricht.

Pretesting

$\dot{V}O_2$max and *W*max were measured on an electronically braked cycle ergometer (Lode, Groningen, Netherlands) during an incremental exhaustive exercise test 1 wk before the first experimental trial (25). These findings were used to determine the 50% *W*max workload that was used in the following trials.

Experimental trials

In a pilot study, we determined plasma HCA concentrations after the ingestion of a single bolus of HCA solution (4.4 g) over a 3.5-h period in 3 male subjects who were not included in the main study. All subjects performed 2 experimental trials consisting of 1 h of supine rest and 2 h of moderate-intensity cycling exercise at 50% *W*max (≈55% $\dot{V}O_2$max). During each trial, subjects ingested a total beverage volume of 12.5 mL/kg body wt. Beverages contained water or water with added HCA. Beverages were provided in randomized order and double blind. All drinks were flavored to camouflage the taste in both trials. Subjects were instructed to refrain from heavy physical labor and recorded their food intake for 2 d before the first trial; these records were used to standardize diet before the second trial. In addition, the evening before each trial, subjects received under supervision a standardized high-carbohydrate meal (85 kJ/kg body wt) that provided 69% of energy as carbohydrate, 15% as fat, and 16% as protein in the laboratory. Thereafter, subjects abstained from food intake and exercise until the trials.

Protocol

Subjects reported to the laboratory at 0800 after an overnight fast. A Teflon catheter (Baxter, Utrecht, Netherlands) was inserted into an antecubital vein. Gas exchange measurements were performed continuously over a 30-min resting period by using a ventilated-hood system (Oxycon β; Mijnhardt, Mannheim, Germany). Thereafter, a blood sample was taken and subjects received the first bolus of test drink ($t = -45$), after which gas exchange measurements were continued for another 30 min. Blood samples were taken at 15-min intervals until $t = 0$. Subjects received a second bolus 15 min before exercise ($t = -15$). After a warming-up period of 5 min at 100 W, subjects started cycling at a moderate intensity of 50% *W*max for 2 h ($t = 0$–120). During exercise, subjects received another bolus of test drink at $t = 30$ and at $t = 60$. During exercise, blood samples were taken at 30-min intervals ($t = 30$ and 60) and breath gases were analyzed every 10 min before a blood sample was taken.

Beverages

All subjects received a total of 0.5 g/kg body wt of a liquid *G. cambogia* extract [Citrimax HCA-450-LS (48% HCA); Interhealth Nutritionals, Benicia, CA] by ingesting 12.5 mL/kg body wt of a 4% solution (38 g/L), which was divided over 4 boluses. This resulted in 18 ± 0.4 g HCA being ingested by every subject in the HCA trial. To diminish the acidity of the solution, 0.1 mol NaOH/L was added for each 1 L of HCA drink. The placebo drink was flavored by adding 20 mg quinine sulfate/L. To improve palatability, both drinks were artificially sweetened by adding 10 mL liquid artificial sweetener containing both cyclamate and saccharine (Natrena BV, Utrecht, Netherlands) for each 1 L of placebo or HCA drink. Beverages were provided in a randomized order and double blind.

Analysis

Blood (7 mL) was collected in EDTA-containing tubes and centrifuged at 1000 × *g* and 4°C for 5 min. Aliquots of plasma were frozen immediately in liquid nitrogen and stored at −40°C. Plasma glucose (Uni Kit III, 07367204; Roche, Basel, Switzerland), lactate (26), fatty acid (Wako NEFA-C kit; Wako Chemicals, Neuss, Germany), and glycerol (UV method, 148270; Boehringer Mannheim GmbH, Mannheim, Germany) concentrations were analyzed with the Cobas Fara semiautomatic analyzer (Roche). Plasma HCA analysis was set up by the TNO Institute, using a Dionex DX500 chromatography system equipped with an IonPac AS 11 column (4.6 × 250 mm; Dionex, Sunnyvale, CA) at a flow rate of 0.002 L/min. HCA was analyzed with a concentration gradient of NaOH starting with 0.5 mmol NaOH/L for 2.5 min, followed by subsequent linear concentration gradients of 0.5–5 mmol NaOH/L in 3.5 min, and 5–38.25 mmol/L NaOH in 12 min. Detection was performed by suppressed conductivity. The same analytic procedure was used to determine the contents of the applied *G. cambogia* extract (Citrimax HCA-450-LS). The water content of this liquid extract was 35% by weight. HCA content was 0.48 g/g extract (48%). The extract further contained small amounts of other organic acids (phosphoric acid and citric acid: 1.7% and 0.9%, respectively), fluoride (0.2%), chloride (2.0%), and sulfate (1.9%). The contents of caffeine and related compounds (theobromine and theophylline) were below the detection threshold (<25 μg/g extract).

Calculations

From the recorded maximal carbon dioxide output ($\dot{V}CO_2$) and $\dot{V}O_2$ (Oxycon-β), total carbohydrate and total fat oxidation rates and energy expenditure were calculated (27) as follows:

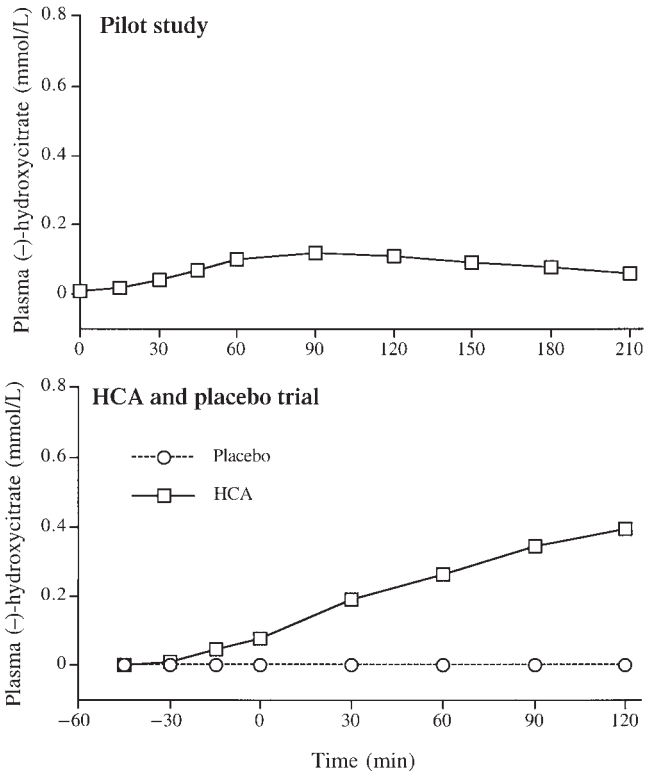

FIGURE 1. Mean (±SEM) plasma (−)-hydroxycitrate (HCA) concentrations in the pilot study after the ingestion of a single dose of HCA (n = 3) and in the HCA and placebo trials (n = 10).

$$\text{Carbohydrate oxidation} = 4.585\,\dot{V}CO_2 - 3.226\,\dot{V}O_2 \quad (1)$$

$$\text{Fat oxidation} = 1.695\,\dot{V}O_2 - 1.701\,\dot{V}CO_2 \quad (2)$$

Statistics

All data are expressed as means ± SEMs. Paired t tests were applied to compare differences in substrate utilization between the placebo and HCA trial. Analysis of variance for repeated measures (with interaction) was performed to study differences over time between trials. A post hoc Scheffe's test was applied in case of a significant F ratio to locate the differences between trials. Statistical significance was set at $P < 0.05$.

RESULTS

In the pilot study, plasma HCA concentrations increased over time after ingestion of a single dose of HCA (4.4 g). Maximal values were attained after 60–90 min (0.12 ± 0.03 mmol/L), after which concentrations decreased (**Figure 1**).

In the main study, plasma HCA concentrations increased up to 0.08 ± 0.01 mmol/L (16.6 mg/L) after the ingestion of 4.4 ± 0.1 g HCA at t = −45 and t = −15 during resting conditions (Figure 1). No HCA was detected in the plasma samples collected in the placebo trial (Figure 1). Respiratory measurements ($\dot{V}O_2$ and $\dot{V}CO_2$) and respiratory exchange ratios (RERs) are illustrated in **Figure 2** and **Figure 3**, respectively. During resting conditions, $\dot{V}O_2$, $\dot{V}CO_2$, and RER were not significantly different between trials and did not change significantly after the ingestion of the first bolus of the HCA or control drink. The relative contribution of fat and carbohydrate oxidation to total energy expenditure is shown in **Figure 4**. Energy expenditure at rest after ingestion of the first bolus of test drink (at t = −15) averaged 5.7 ± 0.6 and 5.7 ± 0.6 kJ/min in the control and HCA trial, respectively. Fat oxidation rates were similar in both trials and averaged 0.07 ± 0.02 and 0.07 ± 0.02 g/min, respectively. Plasma fatty acid, glycerol, glucose, or lactate concentrations are shown in **Figure 5**. No significant differences in plasma fatty acids, glycerol, glucose, and lactate concentrations were observed between the trials at rest.

Plasma HCA concentrations increased further up to 0.39 ± 0.02 mmol/L (82.0 ± 4.8 mg/L) after the ingestion of 4.4 ± 0.1 g HCA after 30 and 60 min of exercise in the HCA trial (Figure 1). $\dot{V}O_2$ and $\dot{V}CO_2$ increased from rest to exercise (Figure 2). RERs tended to decrease over time and averaged 0.857 ± 0.02 and 0.859 ± 0.02 during the second hour of exercise in the control and HCA trial, respectively (Figure 3). Energy expenditure during this period averaged 60.2 ± 5.5 kJ/min in the control and 59.6 ± 5.4 kJ/min in the HCA groups. Fat oxidation was similar in both trials (0.68 ± 0.1 and 0.66 ± 0.1 g/min, respectively) (Figure 4). During exercise, fatty acid and glycerol concentrations increased over time and plasma glucose values tended to decrease (Figure 5). No significant differences between trials were observed for plasma fatty acid, glycerol, and glucose concentrations. Plasma lactate concentrations showed an inital increase during the first 30 min of exercise, after which concentrations stabilized. Significantly lower plasma lactate concentrations were observed in the HCA trial after 30 min of exercise. Throughout the remaining exercise period, lactate concentrations tended to be lower in the HCA trial. However, after 120 min of exercise, plasma lactate concentrations were similar in both trials (Figure 5).

DISCUSSION

In a pilot study, we determined plasma HCA concentrations after the ingestion of 4.4 ± 0.2 g HCA, which is a relatively large amount compared with the small doses applied in previous supplementation studies in humans (24, 28) and advised in commercial weight-loss regimens. To date, only 2 studies (24, 28) have investigated the effects of HCA ingestion in humans, and plasma

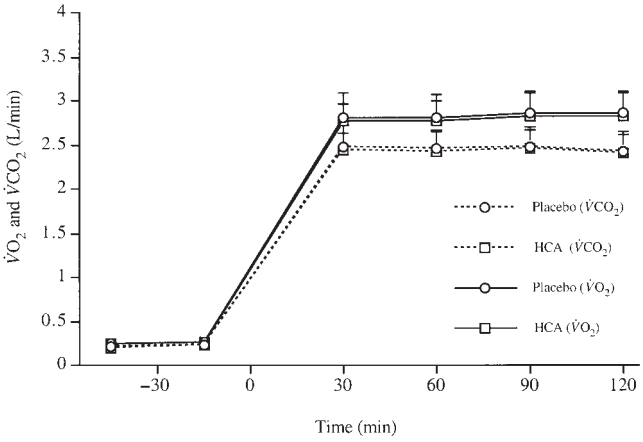

FIGURE 2. Mean (±SEM) oxygen uptake ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$). There were no significant differences between trials. n = 10. HCA, (−)-hydroxycitrate.

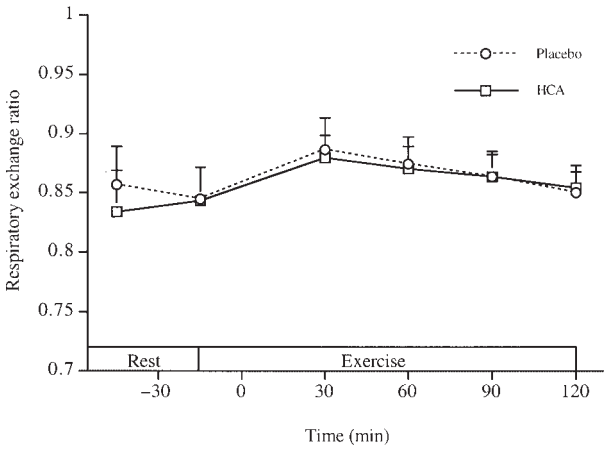

FIGURE 3. Mean (±SEM) respiratory exchange ratios. There were no significant differences between trials. $n = 10$.

HCA concentrations have never been assessed. Therefore, the bioavailability of HCA supplements was the subject of intense debate (9, 11, 12) after the publication of the study by Heymsfield et al (28). The results of our pilot study show that the ingested HCA is absorbed in the gastrointestinal tract and enters the systemic circulation, which is of primary importance if HCA is to reach the target cells and induce its suggested effect on skeletal muscle fuel selection.

To investigate the ability of HCA supplementation to increase skeletal muscle fat oxidation, we provided subjects with a large amount of HCA (a total of 18 ± 0.4 g HCA divided over 4 doses of 4.4 ± 0.1 g) to increase and maintain high plasma HCA concentrations during exercise. Ingestion of the HCA solution resulted in an increase in plasma HCA concentration up to 0.08 ± 0.01 mmol/L during rest, and continued ingestion further increased plasma HCA concentration up to 0.39 ± 0.02 mmol/L during exercise (Figure 1). The amount of HCA ingested (18 ± 0.4 g) in the present study is 6–30 times higher than the doses applied in other studies (24, 28) and prescribed by food supplement producers, which are not based on any scientific literature. In the present study, we applied such a relatively large dose to provide subjects with 10–20% of the amount of HCA that had been administered in the rodent studies.

Although we showed that ingestion of large amounts of HCA results in a substantial increase in plasma HCA concentration, we observed no significant differences in $\dot{V}O_2$ and $\dot{V}CO_2$ at rest or during exercise between the placebo and HCA trial (Figure 2). The gradual increase in fat oxidation during exercise, as indicated by the decrease in RER (Figure 3), was also similar in both trials. Consequently, energy expenditure and fat and carbohydrate oxidation at rest and during exercise were not significantly different between trials (Figure 4). In addition, we did not observe any significant differences in plasma fatty acid, glycerol, or glucose concentrations between trials. We conclude that plasma HCA availability does not increase energy expenditure or stimulate skeletal muscle fat oxidation at rest or during exercise in vivo in endurance-trained humans. It is possible that the absence of an effect on fat oxidation could be explained by the already increased oxidative capacity in the endurance-trained state. However, even in these trained subjects, fat oxidation rates were shown to increase during the 2 h of exercise and, although this is proposed to be caused directly by an exercise-induced decrease in muscle malonyl-CoA concentration (29), plasma HCA availability did not affect these changes in fat oxidation.

During exercise, lactate concentrations tended to be lower in the HCA trial than in the placebo trial during the first 90 min of exercise. The difference was significant only at 30 min (Figure 5). These initial differences could be explained by the fact that HCA has been shown to promote gluconeogenesis in rodent liver (3–8, 30). Potentially, HCA supplementation in the present study increased the rate of lactate conversion to glucose in the liver with a subsequent reduction in plasma lactate concentration. These findings may imply that HCA supplementation affects metabolism in hepatic tissue in humans rather than in skeletal muscle.

HCA administration was shown to significantly inhibit the in vivo and in vitro rates of lipogenesis in rodent liver, adipose tissue, and small intestine (2, 4, 6–8, 15–17), but this has not been confirmed in human tissues. However, de novo lipogenesis is normally regarded as being of little importance in the development of obesity (31, 32). Therefore, in order for HCA to qualify as an effective metabolic antiobesity agent, it should produce a stimulating effect on skeletal muscle fat oxidation or total energy expenditure. In the present study, we showed that HCA supplementation is ineffective in increasing fat oxidation in endurance-trained subjects, even in the large doses. Although in this study only endurance-trained, nonobese subjects were selected, we did not detect any indication that HCA supplementation can affect whole-body metabolism in humans. As such, the only applicability of HCA as an antiobesity agent seems to be the suggested reduction of appetite and food intake (7, 19, 33). However, the pathways by which HCA supplementation could reduce dietary intake remain unclear and there are no data available in the literature that provide any direct evidence for an appetite-suppressing effect and reduced dietary intake after HCA supplementation. These matters remain to be investigated and should include measurement of plasma HCA concentrations to determine whether and to what extent a certain dose of HCA can inhibit dietary intake and be an effective aid in weight-loss studies in humans (9, 11, 12, 28).

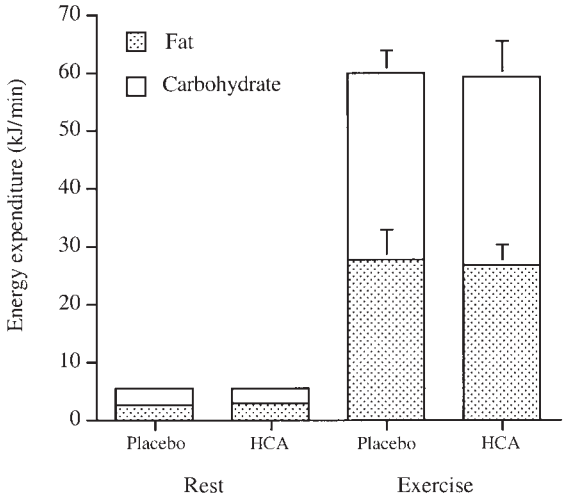

FIGURE 4. Mean (±SEM) energy expenditure at rest and during exercise in the (−)-hydroxycitrate (HCA) and placebo trials. There were no significant differences between trials. $n = 10$.

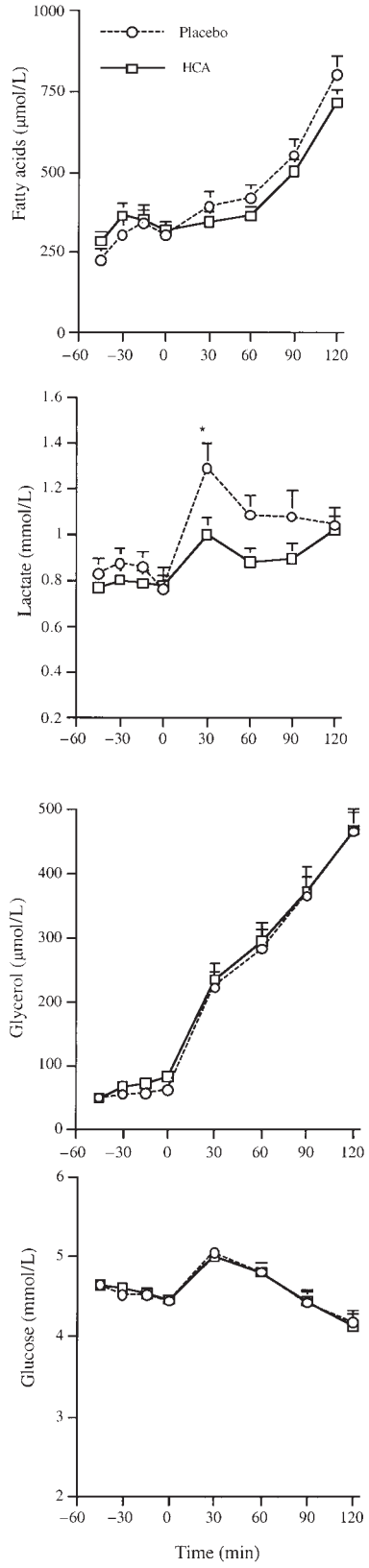

FIGURE 5. Mean (±SEM) plasma (−)-hydroxycitrate (HCA) metabolite concentrations. $n = 10$. *Significantly different from placebo, $P < 0.05$ (analyzed with a two-factor repeated-measures ANOVA with interaction; in the case of a significant F ratio, a post hoc Scheffe's test was applied to locate differences between trials).

In conclusion, this study showed that large doses of *G. cambogia* extract do get absorbed in the intestine and can lead to a substantial increase in plasma HCA concentrations. However, this does not affect fat and carbohydrate oxidation rates at rest or during moderate-intensity exercise in endurance-trained humans. Accordingly, a direct effect of HCA on fat oxidation seems unlikely to contribute to its claimed antiobesity or ergogenic potential.

We gratefully acknowledge the support of Barbara Veldhuis, who performed the plasma HCA measurements.

REFERENCES

1. Triscari J, Sullivan AC. Anti-obesity activity of a novel lipid synthesis inhibitor. Int J Obes 1984;1:227–39.
2. Triscari J, Sullivan AC. Comparative effects of (−)-hydroxycitrate and (+)-allo-hydroxycitrate on acetyl CoA carboxylase and fatty acid and cholesterol synthesis in vivo. Lipids 1977;12:357–63.
3. Sullivan C, Triscari J. Metabolic regulation as a control for lipid disorders. I. Influence of (−)-hydroxycitrate on experimentally induced obesity in the rodent. Am J Clin Nutr 1977;30:767–76.
4. Sullivan AC, Triscari J, Spiegel JE. Metabolic regulation as a control for lipid disorders. II. Influence of (−)-hydroxycitrate on genetically and experimentally induced hypertriglyceridemia in the rat. Am J Clin Nutr 1977;30:777–84.
5. Sullivan AC, Singh M, Srere PA, Glusker JP. Reactivity and inhibitor potential of hydroxycitrate isomers with citrate synthase, citrate lyase, and ATP citrate lyase. J Biol Chem 1977;252:7583–90.
6. Sullivan AC, Triscari J, Hamilton JG, Miller ON, Wheatley VR. Effect of (−)-hydroxycitrate upon the accumulation of lipid in the rat. I. Lipogenesis. Lipids 1974;9:121–8.
7. Sullivan AC, Triscari J, Hamilton JG, Miller ON. Effect of (−)-hydroxycitrate upon the accumulation of lipid in the rat. II. Appetite. Lipids 1974;9:129–34.
8. Sullivan AC, Hamilton JG, Miller ON, Wheatley VR. Inhibition of lipogenesis in rat liver by (−)-hydroxycitrate. Arch Biochem Biophys 1972;150:183–90.
9. Badmaev V, Majeed M, Conte AA. *Garcinia cambogia* for weight loss. JAMA 1999;282:233–4, discussion 235 (letter).
10. Bray GA, Greenway FL. Pharmacological approaches to treating the obese patient. Clin Endocrinol Metab 1976;5:455–79.
11. Firenzuoli F, Gori L. *Garcinia cambogia* for weight loss. JAMA 1999;282:234, discussion 235 (letter).
12. Schaller JL. *Garcinia cambogia* for weight loss. JAMA 1999;282:234, discussion 235 (letter).
13. Szutowicz A, Stepien M, Lysiak W, Angielski S. Effect of (−)hydroxycitrate on the activities of ATP citrate lyase and the enzymes of acetyl-CoA metabolism in rat brain. Acta Biochim Pol 1976;23:227–34.
14. Watson JA, Fang M, Lowenstein JM. Tricarballylate and hydroxycitrate: substrate and inhibitor of ATP: citrate oxaloacetate lyase. Arch Biochem Biophys 1969;135:209–17.
15. Chee H, Romsos DR, Leveille GA. Influence of (−)-hydroxycitrate on lipogenesis in chickens and rats. J Nutr 1977;107:112–9.
16. Lowenstein JM. Effect of (−)-hydroxycitrate on fatty acid synthesis by rat liver in vivo. J Biol Chem 1971;246:629–32.
17. Sugden MC, Watts DI, Marshall CE, McCormack JG. Brown-adipose-tissue lipogenesis in starvation: effects of insulin and (−)-hydroxycitrate. Biosci Rep 1982;2:289–97.
18. McCarty MF. Reduction of free fatty acids may ameliorate risk factors associated with abdominal obesity. Med Hypotheses 1995;44:278–86.
19. McCarty MF. Promotion of hepatic lipid oxidation and gluconeogenesis as a strategy for appetite control. Med Hypotheses 1994;42:215–25.
20. McCarty MF. Optimizing exercise for fat loss. Med Hypotheses 1995;44:325–30.

21. McCarty MF. Inhibition of citrate lyase may aid aerobic endurance. Med Hypotheses 1995;45:247–54.
22. Chen S, Ogawa A, Ohneda M, Unger RH, Foster DW, McGarry JD. More direct evidence for a malonyl-CoA-carnitine palmitoyltransferase I interaction as a key event in pancreatic beta-cell signaling. Diabetes 1994;43:878–83.
23. Ruderman NB, Saha AK, Vavvas D, et al. Malonyl-CoA as a metabolic switch and a regulator of insulin sensitivity. In: Richter EA, Kiens B, Galbo H, Saltin B, eds. Skeletal muscle metabolism in exercise and diabetes. New York: Plenum Press, 1998.
24. Kriketos AD, Thompson HR, Greene H, Hill JO. (−)-Hydroxycitric acid does not affect energy expenditure and substrate oxidation in adult males in a postabsorptive state. Int J Obes Relat Metab Disord 1999;23:867–73.
25. Kuipers H, Verstappen FT, Keizer HA, Geurten P, van Kranenburg G. Variability of aerobic performance in the laboratory and its physiologic correlates. Int J Sports Med 1985;6:197–201.
26. Gutmann I, Wahlefeld AW. L-(+)-Lactate determination with lactate dehydrogenase and NAD. In: Bergmeyer HU, ed. Methods in enzymatic analysis. 2nd ed. New York: Academic Press, 1974: 1464–8.
27. Peronnet F, Massicotte D. Table of nonprotein respiratory quotient: an update. Can J Sport Sci 1991;16:23–9.
28. Heymsfield SB, Allison DB, Vasselli JR, Pietrobelli A, Greenfield D, Nunez C. *Garcinia cambogia* (hydroxycitric acid) as a potential antiobesity agent: a randomized controlled trial. JAMA 1998;280: 1596–600.
29. Winder WW, Arogyasami J, Barton RJ, Elayan IM, Vehrs PR. Muscle malonyl-CoA decreases during exercise. J Appl Physiol 1989; 67:2230–3.
30. Brunengraber H, Boutry M, Lowenstein JM. Fatty acid, 3-beta-hydroxysterol, and ketone synthesis in the perfused rat liver. Effects of (−)-hydroxycitrate and oleate. Eur J Biochem 1978;82:373–84.
31. Schwarz JM, Neese RA, Turner S, Dare D, Hellerstein MK. Short-term alterations in carbohydrate energy intake in humans. Striking effects on hepatic glucose production, de novo lipogenesis, lipolysis, and whole-body fuel selection. J Clin Invest 1995;96:2735–43.
32. Hellerstein MK, Schwarz JM, Neese RA. Regulation of hepatic de novo lipogenesis in humans. Annu Rev Nutr 1996;16:523–57.
33. Hellerstein MK, Xie Y. The indirect pathway of hepatic glycogen synthesis and reduction of food intake by metabolic inhibitors. Life Sci 1993;53:1833–45.